Edition: BP 2025 (Ph. Eur. 11.6 update)

Galantamine Prolonged-release Capsules

General Notices

Galantamine Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Cholinesterase inhibitor; treatment of Alzheimer's disease.

DEFINITION

Galantamine Prolonged-release Capsules contain Galantamine Hydrobromide. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of galantamine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of galantamine, $C_{17}H_{21}NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) To a quantity of the powdered capsule contents containing the equivalent of 4 mg of galantamine, add 10 mL of *acetonitrile* and mix with the aid of ultrasound for 45 minutes. Centrifuge and use the supernatant liquid.
(2) 0.05% w/v of *galantamine hydrobromide BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 8 cm.
(e) After removal of the plate, dry in air and spray with *potassium iodobismuthate solution*, then immediately with *hydrogen peroxide solution (3 per cent)*. Examine the plate in white light.

MOBILE PHASE

1 volume of *glacial acetic acid*, 4 volumes of *butan-1-ol* and 5 volumes of *water*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in *methanol* (50%).

For capsules containing less than 24 mg of galantamine

(1) To 5 whole capsules add a quantity of *acetonitrile* that is equivalent to 20% of the volume of the flask and stir for 30 minutes. Add a quantity of *methanol* equivalent to 30% of the volume of the flask and stir for a further 30 minutes. Add a quantity of 1M *sodium hydroxide* equivalent to 5% of the volume of the flask and mix with the aid of ultrasound. Dilute with *methanol* to produce a solution containing the equivalent of 0.08% w/v of galantamine and filter (a 0.70-µm glass filter is suitable).

For capsules containing 24 mg or more of galantamine

(1) To 7 whole capsules add a quantity of *acetonitrile* equivalent to 20% of the volume of the flask and stir for 30 minutes. Add a quantity of *methanol* equivalent to 30% of the volume of the flask and stir for a further 30 minutes. Add a quantity of 1M *sodium hydroxide* equivalent to 5% of the volume of the flask and mix with the aid of ultrasound. Dilute with *methanol* to produce a solution containing the equivalent of 0.08% w/v of galantamine and filter (a 0.70-µm glass filter is suitable).
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.05% w/v of *galantamine natural for system suitability EPCRS*.
(4) 0.05% w/v of *galantamine synthetic for system suitability EPCRS*.
(5) 0.1% w/v of *galantamine hydrobromide impurity standard BPCRS*.
(6) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (3.5 µm) (Waters XTerra MS C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 55°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *methanol* and 95 volumes of a solution containing 0.079% w/v of *disodium hydrogen orthophosphate dihydrate* and 0.246% w/v of *sodium dihydrogen orthophosphate*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-6	100	0	isocratic
6-20	100→95	0→5	linear gradient
20-35	95→85	5→15	linear gradient
35-50	85→80	15→20	linear gradient
50-51	80→100	20→0	linear gradient
51-60	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to galantamine (retention time about 18 minutes) are: impurity E, about 0.3; impurity 2, about 0.4; impurity 1, about 0.6; impurity C, about 0.8; impurity B, about 1.1; impurity A, about 1.5 and impurity D, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and galantamine is at least 4.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to:

impurities A and E using the chromatogram obtained with solution (3) and the chromatogram supplied with *galantamine natural for system suitability EPCRS*;

impurities C and D using the chromatogram obtained with solution (4) and the chromatogram supplied with *galantamine synthetic for system suitability EPCRS*;

impurities B, 1, and 2 using the chromatogram obtained with solution (5) and the chromatogram supplied with *galantamine hydrobromide impurity standard BPCRS*.

Multiply the area of any peak corresponding to impurity A by a correction factor of 0.5.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.75%);

the area of any peak corresponding to impurity E is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to impurity B or impurity 2 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any peak corresponding to impurity C or impurity D is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4% of each);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (6) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.4% w/v *potassium dihydrogen orthophosphate*, adjusted to pH 6.5 with 5M *sodium hydroxide*.

For capsules containing less than 24 mg of galantamine

(1) To 5 whole capsules add a quantity of *acetonitrile* that is equivalent to 20% of the volume of the flask and stir for 30 minutes. Add a quantity of *methanol* equivalent to 30% of the volume of the flask and stir for a further 30 minutes. Add a quantity of 1M *sodium hydroxide* equivalent to 5% of the volume of the flask and mix with the aid of ultrasound. Dilute with *methanol* to produce a solution containing the equivalent of 0.08% w/v of galantamine and filter (a 0.70-µm glass filter is suitable). Dilute 1 volume of the filtrate to 10 volumes with *methanol (50%)*.

For capsules containing 24 mg or more of galantamine

(1) To 7 whole capsules add a quantity of *acetonitrile* equivalent to 20% of the volume of the flask and stir for 30 minutes. Add a quantity of *methanol* equivalent to 30% of the volume of the flask and stir for a further 30 minutes. Add a quantity of 1M *sodium hydroxide* equivalent to 5% of the volume of the flask and mix with the aid of ultrasound. Dilute with *methanol* to produce a solution containing the equivalent of 0.08% w/v of galantamine and filter (a 0.70-µm glass filter is suitable). Dilute 1 volume of the filtrate to 10 volumes with *methanol (50%)*.
(2) 0.1% w/v of *galantamine hydrobromide BPCRS* in solution A. Dilute 1 volume to 10 volumes with *methanol (50%)*.
(3) 0.05% w/v of *galantamine synthetic for system suitability EPCRS* in *methanol* (50%).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (3.5 µm) (Waters XTerra MS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 55°.
(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *methanol* and 95 volumes of a solution containing 0.079% w/v of *disodium hydrogen orthophosphate dihydrate* and 0.246% w/v of *sodium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and galantamine is at least 4.5.

DETERMINATION OF CONTENT

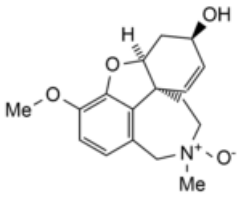
Calculate the content of $C_{17}H_{21}NO_3$ in the capsules using the declared content of $C_{17}H_{21}NO_3$ in *galantamine hydrobromide BPCRS*.

LABELLING

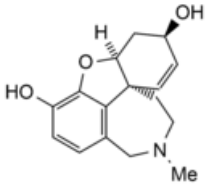
The quantity of active ingredient is stated in terms of the equivalent amount of galantamine.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A to E listed under *Galantamine Hydrobromide* and:



1. galantamine-*N*-oxide



2. *O*-demethylgalantamine